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14. ABSTRACT

Use mission statement for brief factual summary – limit 200 words

The Windber/Walter Reed Clinical Breast Care Project will help lead the way in the 21st Century in the crusade against breast disorders. The project will utilize a multidisciplinary approach as the standard of care for treating breast diseases and breast cancer. Thus multidisciplinary model integrates prevention, screening, diagnosis, treatment and continuing care, but the project is further unique in the incorporation of advances in risk reduction, informatics, tissue banking and research. These efforts will focus on decreasing the morbidity and mortality of breast cancer among American women.

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Tissue Banking, Biomedical Informatics, Focused Research, Translational Research, Genomics, Proteomics, Risk Reduction, Comprehensive Breast Care, Vaccine Development

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Table of Contents

Comprehensive Reproductive System Care Program—Clinical Breast Care Project (CRSCP-CBCP)
Annual Report

1. INTRODUCTION:

The Clinical Breast Care Project (CBCP) is the outcome of the initial FY00 and subsequent Congressional appropriations, and consists of an extensive collaborative effort between Windber Medical Center (Windber, PA – 12th Congressional District of the Honorable John P. Murtha) and Walter Reed Army Medical Center, with funding management by the Henry M. Jackson Foundation for the Advancement of Military Medicine. "The Clinical Breast Care Project (CBCP)" moniker is modified to better reflect its expanded congressional mission, and in FY05 became officially entitled, "The Clinical Breast Care Project of the Comprehensive Reproductive System Care Program". In correspondence, conversation and general usage the shortened form is the "CBCP (of the CRSCP)".

Ultimate Goal of this project: Decrease morbidity and mortality of breast cancer among American Women. Through the interlacing of the five pillars, the CBCP will help lead the crusade against breast disorders.

- Develop a comprehensive breast care center/system that enables health care providers with a multidisciplinary team approach to work toward a common goal.
- Empower women with breast cancer and other breast disorders with the decision-making tools and environment to enhance quality of life and to meet psychosocial needs of the patients and their families.

The five pillars of the CBCP of Walter Reed/Windber are (1) Risk Reduction (2) Focused Research (Genomics and Proteomics); (3) Tissue banking; (4) Biomedical informatics; and (5) Clinical Care.

Pillar Specific Objectives:

1. ***Risk Reduction***:
    - Identify the population of patients at above average risk for the development of breast cancer.
    - Decrease this identified population's rate of breast cancer development.
    - Analyze potential cost differential in the prevention of breast cancer development.

2. ***Focused Research***:
    - Utilize our CBCP-developed panel of microsatellite chromosomal markers to genomically assess various stages of breast disease, malignant and benign, in our on-going effort to elucidate the biologic development timeline of breast cancer.
    - Analyze our in-depth serum and blood repository utilizing various proteomic identification and pattern technologies in our ongoing effort to identify new biomarkers that can be predictive of breast cancer risk and development.
    - Utilize our microarray gene expression profiling capabilities in our effort to analyze the gene expression changes of the continuum of breast disease and cancer development.
    - Analyze the relationship of certain breast cancer protein aspects, eg. ORP-150 protein, to prognosis and other known variables of breast cancer biology.
3. ***Tissue Bank***:
    - Collect and store specimens of breast tissues, lymph nodes, bone marrow aspirates, serum, blood cells (leukocytes), and plasma from every patient undergoing a breast biopsy and/or breast surgery at WRAMC, WMC, MGMC, and LRMC who consent to participate in this study. Use the power of this tissue bank to dramatically further breast disease research.
4. ***Bio-Informatics***:
    - Develop and implement a clinically-relevant prospective, longitudinal computerized database for use in patients with all types of breast care needs.
    - Link this database information through the Internet to data set at a rural primary breast care center with appropriate security and firewall protections.
    - Develop the database to allow for “on-the-fly,” relational, clinically-relevant statistical analysis.
    - Develop an informatics companion to the prospective serum / breast tissue bank.
5. ***Clinical Care***:
    - Decrease the negative psychological impact on the patient of having an evaluation or treatment intervention for breast disease.
    - Create and maintain an environment (medical, physical, psychological) conductive to the multiple needs of the patient undergoing breast disease evaluation / treatment.
    - Utilize objective measurement instruments to longitudinally assess the patient’s psychological response to evaluation and intervention, and base modifications on those results.

Summary of the methodology of the project.
The five pillars of the CBCP of Walter Reed/Windber are (1) Clinical Care; (2) Tissue banking; (3) Risk Reduction; (4) Biomedical informatics; and (5) Focused research (Genomics and Proteomics).

- The clinical care pillar was established by building state of the art breast care facilities at the Windber and Walter Reed sites. These sites were critical to the ability to implement all other pillars of this Project. The Walter Reed Comprehensive Breast Center opened in July 2001, and the Joyce Murtha Breast Center in Windber opened in February 2002.

- The tissue banking pillar was established at both sites in collaboration and entails acquisitions, storage, and movement amongst the sites for research purposes of tissue garnered from all breast surgeries being performed at both locations. The robust IRB-approved protocol that enables this pillar is unique in four critical aspects: It is a tissue usage protocol, not a tissue repository protocol. It is hypothesis-generating, not hypothesis-driven research; It allows for patients to pre-consent for secondary, future uses of the tissues in presently-unknown research; It contains a unique fail-safe mechanism to protect the complete diagnostic integrity of all samples.

- The biomedical informatics effort, is a collaborative development effort between Walter Reed, Windber and Inforsense, driving the development of a comprehensive data warehouse storing clinical and molecular data related to breast disease This is a resource for all CBCP investigators and is exportable for use by other investigators, programs, and organ sites. The data warehouse uniquely integrates clinical data with genomic and proteomic analysis of patient samples and is being extended to incorporate an image repository. This is being developed in close collaboration with industry leaders in the high-end database field, specifically Inforsense and Concentia Digital. Extensive efforts to model the pathways of breast cancer and its risk factors are underway at Windber with consultation from Walter Reed.

- The risk reduction pillar is a vital portion of this mutual project which has resulted in the capability of the project to establish a screening program to identify women who are at high risk for developing breast cancer, and to enter them into a very time- and resource-intensive risk reduction program which can only be appropriately resourced through an appropriation such as this, to decrease significantly these patients' chance of getting breast cancer in the future.

The research aspect is centered on functional genomic/microarrays/proteomics analysis of the tissues and biospecimens, which are acquired as described above. The collaborative research on the functional genomics is established through a high-end microarray, genomics, and proteomics facility at the CBCP Windber Research Institute and will be used as the prime research center for the tissue collaborations, which are developed through this project.

- An important outgrowth of this effort is and will be the bringing of more patients into the Windber and Walter Reed sites for breast cancer evaluations and treatment options; also, the economic development at Windber is being enhanced through job creation and establishment of the scientific research center.

2. BODY:

The CBCP established six primary tasks in its approved Statement of Work for the 2007 fiscal year. These six tasks consist of:

- Task 1. Enroll over 500 patients annually to the "Core" CBCP protocols through consenting in the main CBCP clinical sites.
    a. Core protocols of Tissue and Blood acquisition and molecular testing at the DNA, RNA and Protein level, allied with the clinical and demographic databases

- Task 2. Continuing molecular analysis in CBCP labs, as outlined in the CBCP Core Protocols allowing for global expression analysis of the DNA, RNA and Protein features.
    a. Utilize this repository as the basis for all molecular analysis in CBCP labs, as outlined in the CBCP Core Protocols allowing for global expression analysis of the DNA, RNA, and Protein features.
    b. Utilize this repository as the basis for intramural and extramural collaborations for secondary usage research.

- Task 3: Continuing software development of the CLWS (Clinical Laboratory Workflow System) and its further deployment into the clinical/research arms of the CRSCP-CBCP.

- Task 4. Identifying and counseling no less than 100 high risk patients for development of breast cancer and employ risk reduction strategies.
    a. Perform BRCA gene mutation testing on 10 patients annually in contract with MYRIAD Genetics.

- Task 5. Performing targeted research into genomic analysis of Stages I, II, and III breast cancer, DCIS, LCIS and pre-malignant neoplasia, and presenting findings at national meetings and in peer-reviewed publications.

- Task 6. Perform mass spectrometry fingerprinting of 200 sera samples from patients with diagnosis of breast diseases and analyze for distinct patterns based on disease state.

Task 1: Enrolling over 500 patients in the "core" CBCP protocols.
See section 5 Reportable Outcomes for the breakdown and number of subjects enrolled in "core" CBCP protocols.

Task 2: Continuing molecular analysis in CBCP labs, as outlined in the CBCP Core Protocols allowing for global expression analysis of the DNA, RNA and Protein features.
One of the Core activities of the CBCP is the collection and banking of human biological specimens for research. Tissue specimens are collected from a variety of donors under different conditions. For FY 2007, **554** donors contributed **5,734** samples. The goal is to collect good quality specimens that will provide products such as DNA, RNA and proteins for research. To achieve this goal, the Tissue Banking arm of the CBCP has incorporated the science of Biospecimen Research into its activities. We have performed research studies to determine how temperature changes and time of collection to processing affect the quality of breast specimens collected for research. These findings have been presented at national conferences and are currently being prepared for publication in peer reviewed journals. Our results will contribute to the shaping of the NCI Office of Biorepositories & Biospecimen Research (OBBR)'s Best Practices and their proposed guide lines for specimen collection and processing for tissue banks.

Task 3: Data Warehouse
The patient-centric modularly structured clinical data model for the data warehouse continues to be developed and improved by incorporation of additional questionnaires and data from other clinical and translational projects such as the Gynecological Disease Program. A comparison between our data model with existing models and systems such as SNOMED, MeSH, HL7 has been done, and a comparison with caBIG VCDE has been started. Such comparisons indicated that our data model is unique in supporting clinical and translational research. Issues like how to integrate the information captured from different questionnaires where similar questions may be asked in different ways are being worked on. The interface has been dramatically improved to make it more convenient to use and more powerful for users to interrogate the data from the data warehouse. A manuscript on this development is being prepared.

Currently this data warehouse is playing a pivotal role in supporting research in WRI and WRAMC. We use it for patient cohort formation, specimen selection, and breast cancer risk factor assessment. A number of collaborative projects are under development to make the best use of the data in this data warehouse. With a proof-of-principle pilot project completed, next we will focus on developing molecular study data models in the data warehouse to host the large amount of genomic and proteomic study data.

LIMS (Laboratory Information Management System)
We have identified the LIMS product from Genologics as the system for WRI to adopt. There are two modules commercially available from the company, Geneus for genomic studies, and Proteus for proteomic studies. The company is also developing biomedical informatics modules for clinical data and specimen management. We have worked out with the company that WRI will have early access to the new modules in development.

For implementation of the Geneus and Proteus, we are holding meetings twice a week with Genologics for architecting and planning. As of now, the detailed implementation plan has been developed, a two-server hardware structure has been determined and ordered, a decision on the database is being finalized. In addition, a mock installation has been completed. The plan is to use these two modules to track the data generated in the lab, and at the same time to use the Clinical Laboratory Workflow System, CLWS to keep track of the clinical activities and specimens. Note that the latter is from the previous LIMS from Cimarron software, co-developed by WRI and Cimarron. When the biomedical informatics modules from Genologics are available, all the data tracking will be performed from the backbone structure of Genologics.

In the current structure, the clinical data is directly feeding into the data warehouse. When the Geneus and Proteus are functional, the laboratory data will be fed into the data warehouse as well. This way, the LIMS is for transactional activities, and the data warehouse is for reporting and research purposes. We believe that with this two-separate-system structure, the need for data collection and generation and storage and analysis we will be completely satisfied.

Other current active research and development projects

- **QA measures of the CBCP clinical data:** a set of QA measures have been developed as a collaborative effort between WRI and WRAMC. This includes visual inspection of the completed questionnaires, double blinded data entry, and application of an automated computer program to enforce a metrics of QA rules. A tool called QA Issue Tracking system (QAIT, see next paragraph) is used to track QA issues. A manuscript on these QA measures and results is being finalized.

- **QAIT:** A QA Issue Tracking system has been developed to facilitate communications between data entry at WRI and the clinical data collection/QA team at WRAMC. This web-based system provides centralized management of QA issues with role-based access to related information. It has greatly facilitated the QA process and enhanced overall quality of the CBCP clinical data. A manuscript on this project has been submitted to JAMIA and is currently under revision.
- **Use of the CBCP clinical data warehouse as a research environment for breast cancer risk factor assessment:** The data warehouse and the On-Line Analytical Processing tool as the interface have proven to be a powerful tool in supporting scientific research at WRI and WRAMC. We have tested the idea that the CBCP clinical data warehouse can serve as a research environment for breast cancer risk factor assessment, and have presented the preliminary data at SABCS 2007. Current the draft manuscript has been prepared and is being reviewed by the co-authors.
- **BIOBASE analysis of the differentially expressed genes in normal breast tissues from African American and European American women:** WRI lab scientist Dr. Lori Field has previously reported identification of the set of these differentially expressed genes at AACR. Using the same data set we have performed an in silico transcription factor analysis to explore the possible underlying mechanism why such genes were differentially expressed. The preliminary results have been presented at SABCS 2007 and currently a manuscript is being prepared.
- **Epidemiological Study of Traditional Breast Cancer Risk Factors and Histologically Confirmed Common Breast Pathologies:** A manuscript has been submitted to The Brest Journal and here is the abstract:
We have previously reported that proliferative non-atypical breast disease co-occurs with breast cancer according to non-random patterns. We have speculated that this phenomenon is indicative of a permissive environment for unusual cell proliferation. Elucidation of the risk factors for proliferative breast disease may yield important insight into the early development of micro-environments supportive of breast cancer development. In this report we examine common breast cancer risk factors in association with histologically confirmed common proliferative breast diseases. The study population of 1181 women was drawn from the Clinical Breast Cancer Project Study. *In situ* breast cancer, atypical breast disease, and benign proliferative lesions (sclerosing adenosis, hyperplasia of the usual type, and columnar cell lesions) individually and in combination have similar risk factors to those observed in breast cancer – age, age at menopause, and obesity/never exercising. Age is a significant risk factor for all of these lesions in premenopausal women; age at menopause and obesity or lack of exercise significantly increases the risk of many of these lesions in postmenopausal women. The co-current

presence of at least two benign lesions is associated with similar statistically significant risk factors for *in situ* and atypical breast pathologies in pre-menopausal and post-menopausal women.

Task 4: Identifying and counseling high risk patients for development of breast cancer and employ risk reduction strategies. The risk reduction pillar continues to be a vital portion of this mutual project which has resulted in the capability of the project to establish a screening program to identify women who are at high risk of developing breast cancer, and to enter them into a very time- and resource-intensive risk reduction program which can only be appropriately resourced through an appropriation such as this, to decrease significantly these patients' chance of getting breast cancer in the future. Plans have are in place to expand the risk reduction screening program to the Joyce Murtha Breast Cancer Center in Windber, PA in the coming year. These plans were presented to Congressman John Murtha at the Showcase for Commerce held on May 29 – 30, 2008.

A total of 560 patients were entered into the program this year. The extensive risk assessment, family history and pedigree generation, computerized modeling of individual risk, genetic mutation testing when appropriate (BRCA-1 and BRCA-2), implementation and follow-up of intervention strategies to include chemoprevention, novel diagnostic testing, and even surgical prophylaxis, resulted in a highly successful program where breast cancer truly is being prevented before it ever occurs in many women.

Task 5: Performing targeted research into genomic analysis of Stages I, II, and III breast cancer, DCIS, LCIS and pre-malignant neoplasia, and presenting findings at national meetings and in peer-reviewed publications the period of July 1, 2007 through June 30, 2008. Performing targeted research into genomic analysis of Stages I, II, and III breast cancer, DCIS, LCIS and pre-malignant neoplasia, and presenting findings at national meetings and in peer-reviewed publications the period of July 1, 2007 through June 30, 2008. CBCP continues to have tremendous success in this regard. We have verified that important genetic changes occur across multiple chromosomal regions as breast epithelium transitions from non-neoplastic into neoplastic states. We have identified these changes and published the specific markers for chromosomal loci that we identified as having changed during this transition. Whether or not any of these changes are causal in the malignant transformation process remains to be determined. We are considering, as an organization, whether to seek patent protection for this panel of markers, which may be considered a diagnostic and prognostic marker panel for breast cancer and breast cancer development.
See ATTACHMENT 2 for the list of publications and presentations.

Task 6: Perform mass spectrometry fingerprinting of 200 sera samples from patients with diagnosis of breast diseases and analyze for distinct patterns based on disease state. Perform mass spectrometry fingerprinting of 200 sera samples from patients with diagnosis of breast diseases and analyze for distinct patterns based on disease state. The activities of proteomics facility for the FY07 were mainly centered on the data analysis of Maldi-TOF profiles generated from the acetone processed BC serum samples, planning and implementation of new serum processing workflows to couple them to Maldi-TOF and LC/MS/MS analyses and optimization of workflow for tissue proteomics in collaboration with the PNNL group.

We have applied a simple differential precipitation procedure using acetone to enrich the low molecular wt peptides/proteins from breast cancer serum samples for MALDI-TOF profiling and utilized the MS profile patterns to develop a model that discriminates the two disease groups (benign and invasive) involved in the study. A total of 64 serum samples, evenly divided between benign and invasive cases, were processed by acetone in triplicates and each replicate sample was analyzed twice on MALDI-TOF instrument. The assessment of MS profiles and clinical covariate data yielded 31 benign and 30 invasive cancer cases for comparative analysis. To determine the discriminative features that distinguish benign and invasive cases, both univariate and multivariate analyses were performed on the features. The univariate analysis revealed several features were differentially expressed between benign and invasive BC cases. The unsupervised hierarchical clustering analyses indicate that there were some subgroups among the cancer and benign groups. The discriminative potential of peak clusters was analyzed using a Classification and Regression Tree (CART) algorithm implemented in Ciphergen ProteinChip^{TM} Biomarker Pattern software. CART modeling selects a set of predictors and their interactions that optimally predict the outcome of the dependent variables. Samples were split into 70% training sets and 30% test sets. The menopausal status (categorical variable) was balanced between the benign and invasive groups in the training sets. The average performance of all the predictive models that were built using CART was 50%. The distributions of menopausal status, age, and HRT history for the subjects examined in this study could be discriminated, with statistical significance, between case and control groups. Only the menopausal status was able to be accommodated in the forming of training sets for multivariate analysis. The inability to balance for clinical variables may contribute to inconsistency and high ACE in classification model performance.

We have started a new workflow that supports the parallel processing (96 well plate format) of serum samples using Enchant multi-protein affinity separation kit (Pall Life Sciences) for MaldiTOF and LC/MS/MS profiling. The preliminary

analysis using couple of test serum samples demonstrated good feature rich MALDI-TOF profiles from the processed samples using this workflow. We are planning to couple downstream protein fractionation workflow to the Enchant processed samples for good protein coverage by LC/MS/MS analysis. Alongside this workflow, we are also optimizing the single tube tissue sample preparation for shotgun proteomics of BC tissue samples.

3. ADDITIONAL ACCOMPLISHMENTS

September 2007
A no cost extension was issued extending the period of performance until November 30, 2007.

A retreat with held with Anne Arundel Medical Center (AAMC) on 18 September 2007. Attending from AAMC were; Dr. Tafra, Dr. Cheng, Margaret Matula, the AAMC Clinical Trials Director, Dr.Martin Rosman, the Breast Center Director of Breast Trials, Kathryn Verbanac, PhD, @ ECU, Michelle Waldron and our Fellow, Dr. Elizabeth Feldman. Other attendees were Lee Bronfman, COL Craig Shriver, Dr Jeff Hooke, Leigh Campbell, Dr. Rachel Ellsworth, Dr Darrel Ellsworth, Dr Richard Mural, and Al Kovatich.

Topics of discussion involved the partnership with AAMC and going issues. Future plans were also identified for the partnership. AAMC continued to accrue patients in the past year. Any challenges regarding constraints to the research process flow, from consenting patients to acquiring, storing and shipping biopsecimens, are addressed between Anne Arundel Medical Center staff and Walter Reed Army Medical Center Staff as needed to maintain the high standards of the CBCP biorepository.

October 2007
A meeting was held at USAMRAA on 10 October 2007 to discuss Cooperative Agreement #W81XWH-05-2-0053 “Comprehensive Reproductive System Care Program – Clinical Breast Care Project “(CRSCP). Attendees included; Cheryl Miles – USAMRAA Blue Team Lead, Chris Helman – USAMRAA – Contract Specialist, James Watkins – USAMRAA Contract Officer, Dr. Anne Westbrook – TATRC Contract Officer Representative, Amber Stanley – TATRC – Project Officer, Craig Lebo – TATRC - Chief, Acquisition Strategy, Lee Bronfman – HJF – CBCP Administrative Director, Amy Davis – HJF – Grants Specialist, Dr. Marina Maratos – HJF- Manager, Congressional Programs, Betsy Folk – HJF – VP, Research Administration Services. Topics of discussion involved the period of performance. In 2006, the Period of Performance (POP) on this agreement was extended from 30 June 2006, to 15 September 2006 due to delays in the ASAALT

review of the FY2006 proposal. During this additional timeframe, the program began to utilize funds "at-risk" based on the FY2006 proposed budget. Once the FY2006 funding was awarded, the POP was again extended to 30 September 2007, a full 15 months past the original end date of 30 June 2006. This required CBCP to extend their originally proposed 12 month budget over 15 months in order to support the additional personnel and critical clinical expenses.

With the desire to prevent another 15 month budget extended situation with the FY2007 funds, HJF requested that when USAMRAA issues the continuation modification, the POP only be extended to 30 September 2008. When added to the 2 month no cost extension, this additional 10 months would equal the 12 month proposed POP for the program. USAMRAA agreed that this was possible and would be accommodated.

In order to avoid some of the issues encountered over the past two proposal submissions, TATRC and USAMRAA recommended that HJF submit multi-year proposals and to propose the possibility of increased funding. An example was given of another program that proposed for five years with a proposal value that was double the expected funding. The proposal was crafted to easily separate the core program from the "what-if" additional funding piece of the program. This structure allowed for a one-time review by the MRMC program office, USAMRAA and ASAALT that covered five years of program activity and still allowed for potential funding growth should it become available.
Because CRSCP was already in its 3rd year, it was recommended that the next proposal submission be modified to a proposal with a two-year term (USAMRAA typically runs its agreements no more than five years).
November 2008.

The CBCP conducted the 8th Annual CBCP Offsite 13 – 16 November 2007 at The Wyndham Gettysburg in Gettysburg, PA. Current state of research was presented by various scientists from WRAMC and WRI. Scientific Advisory Board Meeting and strategic planning was conducted during the sessions and the scientific presentations received much positive feedback from the Scientific Advisory Board.

The Clinical Breast Care Project, now in its 8th year, has many notable accomplishments and a promising future. The offsite provides an overview of our key milestones and future goals. Several scientific presentations provided an overview of the current CBCP activities on active projects, findings, and goals. Approximately 100 participants participated in discussions and provided input on the issues posed during the sessions.

December 2008
The San Antonio Breast Cancer Symposium (SABCS) was held 12-15 December 2008. An astounding 17 posters or presentations from the CBCP were presented at the Symposium in San Antonio, TX. See Publication, Abstract and Presentation Data below.

January 2008
Modification P00008, issuing the FY07 funding on January was fully executed on 14 January 2008, after the CBCP proposal was submitted by USAMRAA to ASAALT on 16 August 2007.

COL Shriver was asked to speak at the Military Health System Conference held in Washington DC, 29 January, to illustrate the Military Health System's role in global healthcare delivery. COL Shriver spoke about Walter Reed and the Clinical Breast Care Project taking a clinical microsystem approach when integrating an evidence-based and patient-centered care approach in its Breast Care Center. Attendees can compare and contrast program outcomes before and after implementation of this methodology and consider its implications for use at their facility .

On January 17, 2008 COL Shriver and other CBCP representatives presented an overview of the Clinical Breast Care Project to Altoona Regional Health System (ARHS). ARHS is interested in a possible future partnership with the CBCP.

Dr. Carolyn Compton from the National Cancer Institute met with members of the CBCP on 23 January 2008. Attendees included; Carolyn Compton, MD, PhD, Jim Vaught, PhD, Craig Shriver, MD, Jeffrey Hooke, MD, Tina Progar, Biomedical Informatics Coordinator, Cynthia Gilman, JD, Lee Bronfman, Administrative Director, Richard Mural, PhD, CSO Windber Research Institute

Topics of discussion were the robust CBCP biorepository. Steps were for Dr. Compton to brief Dr. Niederhuber and other NCI leadership. Dr. Compton will meet with NCI attorneys to learn about possible collaboration structure options and plans were discussed to have another face-to-face meeting.
Dr. Compton NIH can begin to develop strategy for public/private collaborations. A working group will develop a strategic plan for future CBCP/NCI collaborations.

February 2008
CBCP participants from WRAMC and WRI visited Pacific Northwest National Laboratory (PNNL) and ISB in Pasco and Seattle Washington 7-8 February 2008. A new proteomics project with collaborators at PNNL was approved and is

ready to begin. This project, with one of the premiere groups in the world headed by Dr. Richard Smith, will take the analysis of CBCP samples to a much deeper lever then previously possible.

May 2008
The Showcase for Commerce was held in Johnstown, PA 29-30 May 2008. COL Shriver shared with Congressman Murtha plans to begin a "Women at High Risk for Breast Cancer" initiative at the Joyce Murtha Breast Care Center in Windber, PA.

June 2008
A task force was formed between the WRAMC Women's Imaging department and the CBCP on 26 January 2008 to explore the feasibility of moving Women's Imaging to the Comprehensive Breast Center and moving administrative staff of breast center to the space currently occupied by Women's Imaging. This would facilitate a World Class, State of the Art Breast Center.

August 2008
The CBCP participated in the TATRC PLR on 19 August 2008.

A management retreat was held 21 August to discuss plans for the submission of the five year BAA which will cover the years 2010 – 2014. Participants included staff from both the WRAMC Breast Center and Windber Research Institute.

Data warehouse
Both the WRI team and InforSense team have made progress on the clinical data model development, which is of a modular structure. At regular meetings, twice a week, terminologies have been defined, a detailed analysis of several objects has been performed and the framework to define a structure that will allow both teams to work on this project in a parallel fashion has been developed. The initial implementation of the hierarchical structure of the relationships between the modules and objects as well as attributes of the clinical data model have been defined and the basic model has been implemented and will be undergoing testing during the next quarter..

New Partners
Facilities continue to express an interest in partnering with the Clinical Breast Care project. St Luke's Cancer Center in Kansas City, MO and Carol Ann Reed Breast Center in Oakland, California have both had core CBCP protocols approved at their respective facilities and we have forwarded their IRB approved protocols to MRMC for secondary review.

4. KEY RESEARCH ACCOMPLISHMENTS

- Gene expression difference have been found between African American women and European American women that may lead to insights into the differences in breast cancer severity seen between these populations.
- Continued studies of low-abundance proteins and peptides that are found in the bloodstream of patients with breast cancer (i.e., an important step in developing a "breast cancer blood test").
- Further enhanced the use of the database and data warehouse system that CBCP has developed for last five years, to integrate the clinical, molecular, pathologic, and biorepository aspects of CBCP translational research. It's robust query capability and analysis tools have assisted in stratifying patients populations for our studies.
- Other developments in the Biomedical informatics core have included development of a new patient centric data model, new tools for microarray data QA, MS data protein peak detection and alignment and an analysis of breast disease co-occurrence.
- Gene expression analysis of primary (node negative) versus primary (node positive) revealed a 70 gene signature distinguishing two types of tumors.
- Gene expression of blood RNA from 100 patients with invasive breast cancer compared to blood RNA from 100 disease free controls has identified several candidate markers of breast cancer detection.
- Specimens continue to be genotyped with a panel of 26 markers that give insight into the stage and prognosis of the tumors.
- A collaboration with Vanderbilt University to examine proteomics differences associated with lymph node metastasis continues and has resulted in the discovery of patterns of protein expression that may distinguish tumors that has lymph node metastasis from those that do not.
- We are currently performing targeted research aimed at identifying blood based biomarkers for the early detection of breast cancer. For this research activity, we are utilizing a multiplex assay platform (xMAP) to analyze a panel of biomarkers made up of matrix metalloproteinase 1, 2 and 9 (known mediators of the extracellular matrix modification) and growth factors. Such a combination will provide positive predictive values that approach 100% compared to the earlier studies that utilized only the matrix metalloproteinases with predictive values of 80%.
- A new collaboration with Pacific Northwest Laboratory (PNNL) has been initiated to use proteomic analysis of breast cancer tissue to identify protein biocarkers for metastasis and disease progression.

5. REPORTABLE OUTCOMES

The CBCP Research Protocols and number of subjects recruited to each for the period July 1 2007 to September 30 2008 are as follows:

Clinical Breast Care Project Walter Reed Army Medical Center

- Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development - **132**
- Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease – **314**

- Molecular Phenotyping of Bone Marrow Aspirates and Peripheral Blood Collected As Part of The Walter Reed Army Medical Center Clinical Breast Care Project (CBCP) – **11**

The Windber Joyce Murtha Breast Care Center Research Protocols and subjects recruited to each is as follows:

- Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development - **111**
- Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease – **157**

Anne Arundel Medical Center Research Protocols and subjects recruited to each is as follows:

- Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease – **115**

Psyco-Social Oncology Services:

A dedicated psychologist counseled 138 patients on an ongoing or crisis basis and sees all diagnosed breast cancer patients attending our Friday template. The services that continue to be provided by this resource are as follows:

- Psycho-social assessment and evaluation of newly diagnosed cancer patients
- For those patients who exhibit a high level of distress, a system has been established that allows close monitoring of patients to include one on one time during chemotherapy.
- Individual and family therapy are available for all breast cancer patients who are in need of support. For patients who live at a distance, telephone sessions are available.

- A Buddy System that provides support to newly diagnosed breast cancer patients from breast cancer patients who have completed treatment.

- On-going psycho-social consultation with patients' medical providers.

A new women's cancer support group began in July 2008 for patients actively being treated for their cancers. The group began with five patients and ended with four patients.

In April 2008, the psychologist collaborated with the National Cancer Institute, Office of Cancer Survivorship and was able to provide the WRAMC patients with a workshop on "How Cancer Can Affect Intimacy". In the fall of 2008 a quarterly presentation series will be made available at WRAMC, through this collaboration, to network with cancer experts in the civilian arena to discuss aspects of cancer pertinent to our work at WRAMC.

Three types of Support Groups are also available:

- A group for patients actively engaged in cancer treatment is provided. The group is a structured 8-week group that meets for 90-minutes once per week. The group format is concrete and offers practical support to patients.
- A group for patients who have completed all treatment. This cancer survivorship group also meets for 8 sessions, 90-minutes, once per week. The format is also concrete and practical.
- A group for parents who have cancer that provides guidance to them to help their children thrive as they overcome cancer. The same format is also used for this group.
- All groups can be conducted in person or via video teleconferencing. Video teleconferencing allows patients who live a distance from Walter Reed, or are too ill to travel a distance, to participate in the support group process.

6. CONCLUSIONS

As we stated in the previous annual report, the next great advances in breast cancer prevention and treatment will be based upon an increased understanding of the changes that occur in the cells of normal breast tissue, as they transition into cancer cells. The CBCP, through its unique and inter-connected 5 pillars,

leverages the strengths of its clinical care arm focusing its research arm to study these cells as they change into cancer. To date, we have been the first to show that the way that breast cancer "behaves", is possibly pre-determined very early in the change of the cells as they are becoming cancerous, as opposed to the cancer cells getting "worse" as they grow and develop. In other words, our important findings are indicating that the behavior of the cancer cells is determined in the development of the cancer, not later. The implications of these findings are critical in our understanding of breast cancer biology, and are leading to new understanding in developing prevention strategies and treatment programs. Our tissue repository has grown into the world's largest and best characterized (annotated) biorepository of human breast tissues, receiving great acclaim from research organizations around the world, and is being shared with other research organizations of great renown, in an effort to speed the pace of discoveries through sharing of this irreplaceable resource. We are finalizing our study into whether or not we can identify "the breast cancer blood test", through the use of serum repository, linked to one of the world's foremost organizations capable of identifying protein patterns in serum from various organ system cancers.

Breast cancer is the most common non-skin cancer in women. It is the single greatest cause of cancer deaths among women under 40, and is a significant cause of mortality for women in the United States Armed Forces. Breast cancer mortality among women <50 years accounts for >40% of years of life lost due to this disease. The economic, social and emotional cost to families is far greater when a young woman dies than when an older woman dies of breast cancer. The more aggressive nature of the disease in young patients along with the attendant costs underscores the importance of early detection of breast cancer in young women. Breast cancer is a curable disease if it is detected early; as such early detection is related to survivorship, cost of treatment and quality of life for the affected woman.

The majority (>90%) of women in active military service are < 40 years of age. The Department of Defense (DOD) with its high percentage of young women and its commitment to health care is particularly concerned about breast cancer. When discovered at a later stage, treatment of breast cancer is expensive, aggressive and results in considerable disruption to the woman's ability to contribute to society. Cost and disruption to life are considerably less when the carcinoma is discovered at an earlier stage. Furthermore, the DOD has a high percentage of African-American (~40%) and Hispanic (~10%) women. Death rates from breast cancer tend to be particularly high in these ethnic groups owing in part to later stage of detection and to the more aggressive nature of breast cancer in these groups.

The active duty military force is approximately 20% female. Most of these service members are in the age range (30-40 years) where routine screening for breast cancer consists only of clinical breast examination. Both mammography and clinical breast examination have a very poor accuracy in the young active duty force in determining which breast abnormalities require treatment, and which are benign and can be left alone.

The immense scale and impact of this problem for the military can be assessed by the fact that there were over 2,000 cases of breast cancer diagnosed in active duty service members over the last ten years (source: ACTURS DoD Tumor Registry data).

Furthermore, there were over 8,000 unnecessary breast biopsies done on active duty women during this time because it takes 4 breast biopsies of normal noncancerous lesions to find each individual breast cancer. Hence, women often need to take lengthy amounts of time off from duty in order to undergo multiple tests leading up to the biopsy as well as time off from duty because of the biopsy itself. This translates into approximately 10,000 weeks, or 30 person-years, of time lost in the evaluation of normal, benign breast lesions in active duty service members. This would be unacceptable for any other healthcare issue, and should be so for this one.

Unfortunately, at the present time there is absolutely no screening tool available currently to diagnose breast cancer in the early, curable stages for women under the age of 40, who make up the vast majority of women in military uniform.

As indicated, approximately 20% of the active duty military force is female, most under the age of 50. Breast cancer strikes one in eight women in her lifetime, and there is a documented change in breast cancer incidence in recent years, such that breast cancer is being detected and diagnosed more often in younger women under the age of 50, and the same is true in our military members. In the same way that diagnostic and therapeutic efforts through the military and US Army are carried out in infectious disease care and research, eg. Malaria, Typhoid, etc., so too must the military address the effects of the scourge of breast cancer and breast diseases on the 20% of total active duty force who are women.

Moreover, CBCP developed and to this day maintains the only specialty breast cancer evaluation and treatment center in the US Army, which is at the CBCP Comprehensive Breast Center at Walter Reed AMC.

Additionally, CBCP is the only Army facility that financially supports direct genetic testing of active duty (all Services) women who are identified in our

Center as being in a high risk category of carrying a BRCA genetic mutation, which when present can signify an up to 90% increased risk of breast cancer development.

CBCP Breast Center is the Army-recognized specialty referral center for active duty personnel from around the globe with medical disorders related to all breast diseases and breast cancer. CBCP Breast Center routinely cares for women on active duty Army from places such as Iraq / OIF, Korea, Europe, and the Far East. CBCP annually cares for over 5,000 patients at its site at Walter Reed.

In summary the Clinical Breast Care Project, a collaborative effort between Walter Reed and Windber, has resulted in excellent working relationships and collaborations between the two sites on all five of the project's main pillars. The project continues to achieve its goals and looks forward to further continuance of this great vision and what will be a national resource, into the future.

7. REFERENCES

N/A

8. APPENDICIES

- ATTACHMENT 1 List of personnel receiving pay from the research effort in FY 2007
- ATTACHMENT 2 : List of publications and meeting abstracts for FY 2007

ATTACHMENT 1

CBCP PERSONNEL RECEIVING PAY FROM THE RESEARCH EFFORT
July 1, 2007 – June 30, 2008

Last Name	First Name	Role	Percent of Effort
Shriver	**Craig**	**Principal Investigator**	**25%**
Basham	Janice	Licensed Practical Nurse	100%
Boone	Jaime	Admin Mgr, CBCP Physician Staff	100%
Bronfman	Eileen	Administrative Director	100%
Campbell	Jamie Leigh	Pathology Assistant	100%
Chestang	Allan	Data Manager	100%
Courville	Faith	Research Nurse	100%
Cronin	Kerri	Receptionist/Administrative Assistant	100%
Del	Ismail	Data Manager	100%
Enowold	Lindsey	Biostatitician	25%
Gutchell	Veronica	Head Nurse, CBCP/ Nurse Practitioner	100%
Hilton	Karrie	Research Nurse	100%
Hodgson	Carol	Nurse Practitioner	100%
Hooke	Jeffrey	Head of Pathology	100%
Kelley	Kay	Research Protocol Coordinator	100%
Means	Marilyn	Lead Medical Clerk/Receptionist	100%
Miller	Donald	Data Manager	100%
Park	Kathleen	Clinical Nurse Specialist	100%
Patterson	Carol	Medical Assistant	100%
Progar	Christina	Biomedical Informatics Coordinator	100%
Reece	Heike	Data Manager	100%
Rojas	Winifred	Lab Tech/Phlebotomist	100%
Rosenquist	Monica	Budget Analyst	100%
Stojadinovic	Alexander	Breast Surgeon	25%
Vilakasi	Patricia	Research Nurse	100%
Williamson	Eric	Clinic Administrator	100%
Zhao	Xinyan	Histology Technician	100%
Zhu	Kangmin	Epidemiologist	20%

ATTACHMENT 2

PUBLICATION, ABSTRACT AND PRESENTATION DATA

July 1, 2007 – September 30, 2008

PUBLICATIONS – 2008

Maskery SM, Hu H, Hooke J, Shriver CD, Liebman MN. **"A Bayesian Derived Network of Breast Pathology Co-Occurrence".** Journal of Biomedical Informatics. In print 2008

Becker TE, Ellsworth RE, Deyarmin B, Patney HL, Jordan RM, Hooke JA, Shriver CD. Ellsworth DL. **"Genomic Heritage of Lymph Node Metastases: Implications for Clinical Management of Patients with Breast Cancer."** Clinical Biochemistry Journal, Mar 08 submitted

Maskery SM, Hu H, Hooke J, Shriver CD, Liebman MN. **"A Bayesian Derived Network of Breast Pathology Co-Occurrence".** Journal of Biomedical Informatics. In print 2008

PRESENTATIONS – 2008

Ellsworth RA, Patney HL, Ellsworth DL, Love B, Deyarmin B, Hooke JA, Shriver CD. **"Genomic Alterations Associated with Early Stages of Breast Tumor Metastasis."** Society of Surgical Oncology, May 2008, Chicago, IL

ABSTRACTS – 2008

Shriver CD. **"Star Wars Defense Battles Breast Cancer."** Press Release Conjoint Royal Australasian College of Surgeons and the College of Surgeons of Long Kong, May 08

Shriver CD. **"Well-documented Breast Cancer Tissue Collection Meets High Throughout Proteomics to Find Aggressive-tumor Markers in Blood."** Press Release, PNNL, May 08

Shoemaker A, Heckman C, Zhang Y, Colledge A, Deyarmin B, Kane J, Hooke J, Shriver C, Mural R, Somiari S. **"RNA Quality of Human Breast Tissue after Surgical Removal-Effect of Processing Method, Temperature and Storage."** ISBER, Bethesda, MD, May 18-21, 2008

Fields L. **"Gene Expression Differences in Primary Breast Tumors from African American and Caucasian women."** AACR 12-16 Apr 08 San Diego

Somiari SB, Kovatich AJ, Zhang Y , Baran PN, Deyarmin B, Kane J, Hooke J, Mural R, Shriver CD. **"The Prognostic Role of Cell Cycle Regulators in Invasive Breast Cancer."** AACR April 12-16th, 2008 San Diego

Shoemaker A, Heckman C, Zhang Y, Colledge A, Deyarmin B, Kane J, Hooke J, Shriver C, Mural R, Somiari S. **"The Prognostic Role of Cell Cycle Regulators in Invasive Breast Cancer."** AACR, April 12-16th, 2008 San Diego

Ellsworth RE, Hooke JA, Shriver CD. **"Effect of Equal-Access to Breast Care on Clinicopathological Phenotypes of Invasive Breast Tumors in African American"**. AACR, 12-16 Apr 08, San Diego

Stojadinovic A, **"Assessment of Circulating of Tumor Cells (CTCs) for Monitoring Immediate and Long-Term Response to Primary and Booster Inoculations with a Preventative HER2/neu Vaccine in Breast Cancer Patients".** AACR 12-16 Apr 08, San Diego

Ellsworth DL, Ellsworth RE, Patney HL, Becker TE, Deyarmin B, Hooke JA, Shriver CD. **"Molecular Heterogeneity Among Sentinel Lymph Node Metastases: Implications for the Sentinel Node Hypothesis."** Breast Cancer Symposium 5-7 Sep 08, Washington, DC

PUBLICATIONS – 2007

Ellsworth RE, Hooke JA, Love B, Ellsworth DL, Shriver CD. "**Contribution of Chromosomal Alterations to the Development of Poorly-Differentiated Invasive Breast Carcinomas**". Am Journ of Surg Path, submitted Dec 07.

Stojadinovic A, Hooke JA, Shriver CD, Nissan A, Kovatich AJ, Kao TC, Ponniah S, Peoples GE, Moroni M. "**HYOU1/Orp150 Expression in Breast Cancer**". Intern Medical Journ of Experimental & Clin Research, Oct 2007. Out for print.

Bronfman L, Shriver CD, Gutchell E. "**The Clinical Perspective**". Chapter 2, Biomedical Informatics: A Translational Approach, submitted Aug 2007.

Field LA, Jordan RM, Hadix JA, Dunn MA, Shriver CD, Ellsworth RE, Ellsworth DL. "**Functional Identity of Genes Detectable in Expression Profiling Assays Following Globin mRNA Reduction of Peripheral Blood Samples**". Clin Biochem 2007;40:499-502.

Ellsworth RE, Ellsworth DL, Love B, Patney H, Hoffman L, Kane J, Hooke J, Shriver CD. "**Correlation of Levels and Patterns of Genomic Instability with Histological Grading of DCIS**". Annals of Surg Onc.

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Maskery SM, Hu H, Shriver CD, Liebman MN. "**A Bayesian Derived Network of Breast Pathology Diagnoses**". Jour of Biomed Informatics. Submitted Dec 07.

Vizza J, Neatrour DM, Felton PM, Ellsworth DL. **Improvement in psychosocial functioning during an intensive cardiovascular lifestyle modification program.** J Cardiopulm Rehabil 2007; (in press).

Becker TE, Ellsworth RE, Deyarmin B, Patney HL, Jordan RM, Hooke JA, Shriver CD, Ellsworth DL. **Genomic heritage of axillary lymph node metastases in breast cancer patients**. Ann Surg Oncol (submitted).

Croft DT Jr, Jordan RM, Patney HL, Shriver CD, Vernalis MN, Orchard TJ, Ellsworth DL. **Performance of whole-genome amplified DNA isolated from serum and plasma on high density single nucleotide polymorphism arrays**. J Mol Diagn (submitted).

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Ellsworth RE, Bronfman L, Gutchell V, Love B, Field LA, Weyandt JD, Shriver CD. "**The Clinical Breast Care Project: An Important Resource in Investigating Environmental and Genetic Contributions to Breast Cancer in African American Women**". Cell and Tissue Banking, e-pub, 2007.

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PRESENTATIONS – 2007

Ellsworth DL, Seeley EH, Ellsworth RE, Deyarmin B, Sanders ME, Hooke JA, Caprioli RM, Shriver CD. "**Tumor Microenvironment in Breast Cancer Metastasis: Direct Tissue Protein Profiling of Tumor-Associated Stroma from Invasive Breast Cancer Patients with versus without Axillary Lymph Node Metastasis**". SABCS, Dec 13-16, 2007.

Hu H. Informatics infrastructure development for translational research. Main Speaker at the "**Unlock Insight from Your Clinical Data**"— Joint world-wide WebEx by InforSense and the Windber Research Institute, September 19, 2007.

Hu H: **"A Modularly Structured Clinical Data Warehouse."** *Clinical Breast Care Project Offsite Meeting*. November 13-16, 2007.

Hu H, Organizer of the Panel Discussion **"Data Collection and Generation in CBC".** *Clinical Breast Care Project Offsite Meeting*. November 13-16, 2007.

ABSTRACTS – 2007

Ellsworth DL, Ellsworth RE, Patney HL, Becker TE, Deyarmin B, Jordan RM, Hooke JA, Shriver CD. "**Primary Tumor Heterogeneity and Sentinel Lymph Node Metastasis: Understanding Molecular Processes of Breast Cancer Metastasis**". SABCS, Dec 13-16, 2007.

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Zhang Y, Weihong S, Gutchell EM, Mural RJ, Shriver CD, Liebman MN,Hu H. "**An Issue Tracking System to Facilitate the Enhancement of Clinical Data Quality in the Clinical Breast Care Project**". AMIA 2007 Annual Symposium November 10-14, 2007, Chicago, IL

Ellsworth RE, Weyandt JD, Patney HL, Anthony K, Shriver CD. "**Identification of cSNPs in Environmental Response Genes Contributing to Breast Cancer**". Am Soc of Hum Genetics, Oct 23-27, 2007.

Ellsworth RE, Hooke JA, Shriver CD. "**Pathological Characteristics of Breast Tumors in African American Women Treated Within An Equal-Access Health-Care System: Biological and Molecular Contributions to the Aggressive Phenotype and Poor Clinical Outcomes**". SSO, Sep 2007.

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Liebman MN, Deyarmin B, Shriver CD, Stegmaier P, Karas H, Kel A, Wingender E. "**Analysis of HER2/neu as a Diagnostic/Biomarker using ExPlain to Examine Signaling Pathways and Transcription Factors**". 15th Annual Intern Conf on Intell Systems for Molecular Biology & 6th European Conf on Computational Biology, Vienna, Austria, July 21-25, 2007.

Hu H, Correll M, Osmond M, Gao J, Oleynikov A, Sheldon J, Kvecher L, Mural RJ, Shriver CD, Liebman MN. "**A clinical data warehouse to support translational research**". 15th Annual International Conference on Intelligent Systems for Molecular Biology (ISMB), July 21-25, 2007, Vienna, Austria.

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In addition to the above list of publications and presentations, our collaborator Windber Research Institute has participated in the following publications and presentations.

PEER-REVIEWED PUBLICATIONS

Jordan R, Patel S, Hu H, and Lyons-Weiler J: Consistency analysis of competing tests for finding differentially expressed genes in lung adenocarcinoma. *Cancer Informatics (in press).*

Yang S, Guo X, and Hu H: MOF—an R function to detect microarray outlier slides. *Genomics, Proteomics and Bioinformatics (in press).*

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Hong-Wen Deng, Hui Shen, Yongjun Liu, and Hai Hu (Editors). *Current Topics in Human Genetics: Studies of Complex Diseases*. World Scientific Publishing Co. 2007.

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CONFERENCE PRESENTATIONS AND INVITED SPEECHES

Hu H: Application of biomedical informatics to translational research. The First Annual EITC-Bio Workshop. June 7, 2008. Princeton University, Princeton, NJ. Invited speaker.
Hu H: Synergy of informatics and biomedical research in academia and industry. The First Annual EITC-Bio Workshop. June 7, 2008. Princeton University, Princeton, NJ. Invited panelist.